AMENDMENTS TO THE SPECIFICATION:

Please amend the specification as follows:

[026] The TrkB receptor agonists include neurotrophic factors that activate a TrkB receptor, such as a Brain ~~Derivated~~Derived Neurotrophic Factor or a Neurotrophin 4. The TrkB receptor agonists can also include antibodies that bind to TrkB receptors and activate them. These methods of using TrkB receptor agonists provide useful methods for enhancing the neuronal transport of a tetanus toxin or a tetanus toxin fusion protein.

[027] The TrkB receptor antagonists include antibodies that bind to a TrkB receptor agonist, such as those described above, and thereby decrease the activation of a TrkB receptor. For example, these antibodies can be directed to neurotrophic factors that activate a TrkB receptor, such as a Brain ~~Derivated~~Derived Neurotrophic Factor or a Neurotrophin 4. In addition, TrkB receptor antagonists include antibodies that bind to TrkB receptors and inactivate them. These methods of using TrkB receptor agonists provide useful methods for decreasing or preventing the neuronal transport of a tetanus toxin or a tetanus toxin fusion protein.

[034] The present invention also provides compositions comprising a TrkB receptor agonist or a GFR*α*/cRET receptor agonist and a fusion protein comprising a fragment C of the tetanus toxin fused to a second protein. In one embodiment, the TrkB agonist is a neurotrophic factor such as a Brain ~~Derivated~~Derived Neurotrophic Factor or a Neurotrophin 4. In another embodiment, the GFR*α*/cRET receptor agonist is a neurotrophic factor, such as Glial-Derived Neurotrophic Factor

[036] **FIGURE 1** shows the DNA sequence [SEQ ID NO:1] and amino acid sequence [SEQ ID NO:2] of the TTC fragment cloned in pBS:TTC.

[0115] We have also previously shown that, without neural activity, localization of a TTC fusion protein at the NMJ is impaired (Miana-Mena et al., 2002). In this aspect of the invention, therefore, we investigated *in vivo*, the influence of neurotrophic factors on neuronal localization and internalization of GFP-TTC and the mechanisms by which certain neurotrophic factors influence neuronal trafficking *in vivo*. We found that localization of GFP-TTC at the NMJ is rapidly induced by neurotrophic factors such as Brain ~~Derivated~~Derived Neurotrophic Factor (BDNF), Neurotrophin 4 (NT-4), and Glial-Derived Neurotrophic Factor (GDNF) but not by Nerve Growth Factor (NGF), Neurotrophin 3 (NT-3), and Ciliary Neurotrophic Factor (CNTF).

[0116] Co-injection of various amounts of BDNF with the GFP-TTC probe induces an increase of the fluorescence measured at the neuromuscular junction (NMJ). This effect, which is detectable as early as 5 min after injection and reaches a maximum level at about 30 min after injection, indicates that BDNF treatment enhances neuronal endocytosis. Among other functions, BDNF stimulates the secretion of neurotransmitter from *Xenopus* nerve muscle co-cultures and from hippocampal neurons (Lohof et al., 1993; Tyler and Pozzo-Miller, 2001). Since tetanus toxin is known to enter neurons by means of synaptic vesicle endocytosis (Matteoli et al., 1996), BDNF might increase GFP-TTC internalization through enhancement of synaptic vesicle turnover. In our study, BDNF effects persisted after BoTx/A treatment, which blocks exocytosis and endocytosis of synaptic vesicles, showing that BDNF increases the kinetics and localization of a TTC-containing fusion protein at the NMJ through another

endocytic pathway. Therefore, intramuscular injection of GFP-TTC and visualization of transport mechanisms revealed at least two different endocytic pathways: a clathrin-dependent and a clathrin-independant pathway. We found that after intramuscular injection of GFP-TTC, it displayed characteristics consistent with localization in lipid rafts, including biochemical colocalization with caveolin 3 and colocalization with GM1, a raft marker identified by CT-b binding (Orlandi and Fishman, 1998; Wolf et al., 1998). Accordingly, the clathrin-independent pathway used by GFP-TTC, appears to involve lipid microdomains. Analysis by confocal microscopy revealed morphologically two different labelings. Firstly, a GFP-TTC diffuse staining, which partially overlaps with the synaptic vesicle SV2 but also with the raft marker CT-b, indicating a mixing of synaptic vesicles and lipid rafts. Secondly, highly fluorescent domains, which are detected before and persist after the more diffuse pattern and that appear to be invaginations or infoldings of the synaptic membrane. These GFP-TTC patches contained only CT-b labeling. Indeed, lipid microdomains, which play a role in cellular functions such as vesicular trafficking and signal transduction (Simons and Toomre, 2000), can move laterally and cluster into larger patches (Harder et al., 1998). They might also be specific zones of exocytosis in the presynaptic compartment, undergoing a rapid form of internal traffic in response to retrograde signaling from target cells. Similar infolding and cisternae structures have been described in frog motor nerve terminals, which ~~replesnish~~replenish the pool of synaptic vesicles in a manner dependent upon neuronal activity (Richards et al., 2000). In CHO cells, tubular caveolae have also been described (Mundy et al., 2002).

[0129] We also examined the effect of five additional trophic factors on GFP-TTC localization at the NMJ, including the neurotrophins NT-3 ; NT-4 and NGF as well as the neurocytokine CNTF (Ciliary Neurotrophic Factor), a member of the LIF cytokine family, and GDNF (Glial ~~Derivated~~Derived Neurotrophic Factor), a member of the TGF-ß superfamily (Table 2). Many BDNF actions in neurons are mediated *via* the high affinity receptor tyrosine kinase TrkB, which is also the receptor for NT-4. Like BDNF, NT-4 also induced GFP-TTC localization at the NMJ (a 1.54 ± 0.23 fold increase). A level of induction similar to NT-4 was also observed for GDNF (Table 2). On the other hand, even at high concentrations, neither NGF, NT-3, nor CNTF exhibited a significant effect on GFP-TTC localization.